Exhibit 3

CHAPTER 3.2

SKIN CORROSION/IRRITATION

3.2.1 Definitions and general considerations

3.2.1.1 *Skin corrosion* refers to the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis occurring after exposure to a substance or mixture.

Skin irritation refers to the production of reversible damage to the skin occurring after exposure to a substance or mixture.

3.2.1.2 To classify, all available and relevant information on skin corrosion/irritation is collected and its quality in terms of adequacy and reliability is assessed. Wherever possible classification should be based on data generated using internationally validated and accepted methods, such as OECD Test Guidelines or equivalent methods. Sections 3.2.2.1 to 3.2.2.6 provide classification criteria for the different types of information that may be available.

3.2.1.3 A *tiered approach* (see 3.2.2.7) organizes the available information into levels/tiers and provides for decision-making in a structured and sequential manner. Classification results directly when the information consistently satisfies the criteria. However, where the available information gives inconsistent and/or conflicting results within a tier, classification of a substance or a mixture is made on the basis of the weight of evidence within that tier. In some cases when information from different tiers gives inconsistent and/or conflicting results (see 3.2.2.7.3) or where data individually are insufficient to conclude on the classification, an overall weight of evidence approach is used (see 1.3.2.4.9 and 3.2.5.3.1).

3.2.1.4 Guidance on the interpretation of criteria and references to relevant guidance documents are provided in 3.2.5.3.

3.2.2 Classification criteria for substances

Substances can be allocated to one of the following three categories within this hazard class:

(a) Category 1 (skin corrosion)

This category may be further divided into up to three sub-categories (1A, 1B and 1C) which can be used by those authorities requiring more than one designation for corrosivity.

Corrosive substances should be classified in Category 1 where sub-categorization is not required by a competent authority or where data are not sufficient for sub-categorization.

When data are sufficient, and where required by a competent authority, substances may be classified in one of the three sub-categories 1A, 1B or 1C.

(b) Category 2 (skin irritation)

(c) Category 3 (mild skin irritation)

This category is available for those authorities that want to have more than one skin irritation category (e.g. for classifying pesticides).

3.2.2.1 *Classification based on human data*

Existing reliable and good quality human data on skin corrosion/irritation should be given high weight where relevant for classification (see 3.2.5.3.2) and should be the first line of evaluation, as this gives information directly relevant to effects on the skin. Existing human data could be derived from single or repeated exposure(s), for example in occupational, consumer, transport or emergency response scenarios and epidemiological and clinical studies in well-documented case reports and observations (see 1.1.2.5 (c), 1.3.2.4.7 and 1.3.2.4.9). Although human data from accident or poison centre databases can provide evidence for classification, absence of incidents is not itself evidence for no classification, as exposures are generally unknown or uncertain.

3.2.2.2 ***Classification based on standard animal test data***

OECD Test Guideline 404 is the currently available internationally validated and accepted animal test for classification as skin corrosive or irritant (see Tables 3.2.1 and 3.2.2, respectively) and is the standard animal test. The current version of OECD Test Guideline 404 uses a maximum of 3 animals. Results from animal studies conducted under previous versions of OECD Test Guideline 404 that used more than 3 animals are also considered standard animal tests when interpreted in accordance with 3.2.5.3.3.

3.2.2.2.1 *Skin corrosion*

3.2.2.2.1.1 A substance is corrosive to skin when it produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least one tested animal after exposure for up to 4 hours.

3.2.2.2.1.2 For those authorities wanting more than one designation for skin corrosion, up to three sub-categories are provided within the corrosion category (Category 1, see Table 3.2.1): sub-category 1A, where corrosive responses are noted following up to 3 minutes exposure and up to 1 hour observation; sub-category 1B, where corrosive responses are described following exposure greater than 3 minutes and up to 1 hour and observations up to 14 days; and sub-category 1C, where corrosive responses occur after exposures greater than 1 hour and up to 4 hours and observations up to 14 days.

Table 3.2.1: Skin corrosion category and sub-categories

	Criteria
Category 1	Destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least one tested animal after exposure ≤ 4 h
Sub-category 1A	Corrosive responses in at least one animal following exposure ≤ 3 min during an observation period ≤ 1 h
Sub-category 1B	Corrosive responses in at least one animal following exposure > 3 min and ≤ 1 h and observations ≤ 14 days
Sub-category 1C	Corrosive responses in at least one animal after exposures > 1 h and ≤ 4 h and observations ≤ 14 days

3.2.2.2.2 *Skin irritation*

3.2.2.2.2.1 A substance is irritant to skin when it produces reversible damage to the skin following its application for up to 4 hours.

3.2.2.2.2.2 An irritation category (Category 2) is provided that:

(a) recognizes that some test materials may lead to effects which persist throughout the length of the test; and

(b) acknowledges that animal responses in a test may be variable.

An additional mild irritation category (Category 3) is available for those authorities that want to have more than one skin irritation category.

3.2.2.2.2.3 Reversibility of skin lesions is another consideration in evaluating irritant responses. When inflammation persists to the end of the observation period in 2 or more test animals, taking into consideration alopecia (limited area), hyperkeratosis, hyperplasia and scaling, then a material should be considered to be an irritant.

3.2.2.2.2.4 Animal irritant responses within a test can be variable, as they are with corrosion. A separate irritant criterion accommodates cases when there is a significant irritant response but less than the mean score criterion for a positive test. For example, a test material might be designated as an irritant if at least 1 of 3 tested animals shows a very elevated mean score throughout the study, including lesions persisting at the end of an observation period of normally 14 days. Other responses could also fulfil this criterion. However, it should be ascertained that the responses are the result of chemical exposure. Addition of this criterion increases the sensitivity of the classification system.

3.2.2.2.2.5 An irritation category (Category 2) is presented in Table 3.2.2 using the results of animal testing. Authorities (e.g. for classifying pesticides) also have available a less severe mild irritation category (Category 3). Several criteria distinguish the two categories (Table 3.2.2). They mainly differ in the severity of skin reactions. The

major criterion for the irritation category is that at least 2 of 3 tested animals have a mean score of ≥ 2.3 and ≤ 4.0. For the mild irritation category, the mean score cut-off values are ≥ 1.5 and < 2.3 for at least 2 of 3 tested animals. Test materials in the irritation category are excluded from the mild irritation category.

Table 3.2.2: Skin irritation categories [a,b]

Categories	Criteria
Irritation (Category 2) (applies to all authorities)	(1) Mean score of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.
Mild irritation (Category 3) (applies to only some authorities)	Mean score of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions (when not included in the irritant category above).

[a] *Grading criteria are understood as described in OECD Test Guideline 404.*

[b] *Evaluation of a 4, 5 or 6-animal study should follow the criteria given in 3.2.5.3.3.*

3.2.2.3 *Classification based on in vitro/ex vivo data*

3.2.2.3.1 The currently available individual *in vitro/ex vivo* test methods address either skin irritation or skin corrosion, but do not address both endpoints in one single test. Therefore, classification based solely on *in vitro/ex vivo* test results may require data from more than one method. For authorities implementing category 3 it is important to note that the currently available internationally validated and accepted *in vitro/ex vivo* test methods do not allow identification of substances classified as category 3.

3.2.2.3.2 Wherever possible classification should be based on data generated using internationally validated and accepted *in vitro/ex vivo* test methods, and the classification criteria provided in these test methods needs to be applied. *In vitro/ex vivo* data can only be used for classification when the tested substance is within the applicability domain of the test methods used. Additional limitations described in the published literature should also be taken into consideration.

3.2.2.3.3 *Skin corrosion*

3.2.2.3.3.1 Where tests have been undertaken in accordance with OECD Test Guidelines 430, 431, or 435, a substance is classified for skin corrosion in category 1 (and, where possible and required into sub-categories 1A, 1B or 1C) based on the criteria in Table 3.2.6.

3.2.2.3.3.2 Some *in vitro/ex vivo* methods do not allow differentiation between sub-categories 1B and 1C (see Table 3.2.6). Where sub-categories are required by competent authorities and existing *in vitro/ex vivo* data cannot distinguish between the sub-categories, additional information has to be taken into account to differentiate between these two sub-categories. Where no or insufficient additional information is available, category 1 is applied.

3.2.2.3.3.3 A substance identified as not corrosive should be considered for classification as skin irritant.

3.2.2.3.4 *Skin irritation*

3.2.2.3.4.1 Where classification for corrosivity can be excluded and where tests have been undertaken in accordance with OECD Test Guideline 439, a substance should be considered for classification as skin irritant in category 2 based on the criteria in Table 3.2.7.

3.2.2.3.4.2 Where competent authorities adopt category 3, it is important to note that currently available *in vitro/ex vivo* test methods for skin irritation (e.g. OECD Test Guideline 439) do not allow for classification of

substances in category 3. In this situation, if the classification criteria for either category 1 or 2 are not fulfilled, additional information is required to differentiate between category 3 and no classification.

3.2.2.3.4.3 Where competent authorities do not adopt category 3, a negative result in an internationally accepted and validated *in vitro/ex vivo* test for skin irritation, e.g. OECD Test Guideline 439, can be used to conclude as not classified for skin irritation.

3.2.2.4 ***Classification based on other, existing skin data in animals***

Other existing skin data in animals may be used for classification, but there may be limitations regarding the conclusions that can be drawn (see 3.2.5.3.5). If a substance is highly toxic via the dermal route, an *in vivo* skin corrosion/irritation study may not have been conducted since the amount of test substance to be applied would considerably exceed the toxic dose and, consequently, would result in the death of the animals. When observations of skin corrosion/irritation in acute toxicity studies are made, these data may be used for classification, provided that the dilutions used and species tested are relevant. Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes. This is generally indicated in the standardised test methods. Guidance on the use of other existing skin data in animals including acute and repeated dose toxicity tests as well as other tests is provided in 3.2.5.3.5.

3.2.2.5 ***Classification based on chemical properties***

Skin effects may be indicated by pH extremes such as ≤ 2 and ≥ 11.5 especially when associated with significant acid/alkaline reserve (buffering capacity). Generally, such substances are expected to produce significant effects on the skin. In the absence of any other information, a substance is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5. However, if consideration of acid/alkaline reserve suggests the substance may not be corrosive despite the low or high pH value, this needs to be confirmed by other data, preferably from an appropriate validated *in vitro/ex vivo* test. Buffering capacity and pH can be determined by test methods including OECD Test Guideline 122.

3.2.2.6 ***Classification based on non-test methods***

3.2.2.6.1 Classification, including the conclusion not classified, can be based on non-test methods, with due consideration of reliability and applicability, on a case-by-case basis. Such methods include computer models predicting qualitative structure-activity relationships (structural alerts, SAR); quantitative structure-activity relationships (QSARs); computer expert systems; and read-across using analogue and category approaches.

3.2.2.6.2 Read-across using analogue or category approaches requires sufficiently reliable test data on similar substance(s) and justification of the similarity of the tested substance(s) with the substance(s) to be classified. Where adequate justification of the read-across approach is provided, it has in general higher weight than (Q)SARs.

3.2.2.6.3 Classification based on (Q)SARs requires sufficient data and validation of the model. The validity of the computer models and the prediction should be assessed using internationally recognised principles for the validation of (Q)SARs. With respect to reliability, lack of alerts in a SAR or expert system is not sufficient evidence for no classification.

3.2.2.7 ***Classification in a tiered approach***

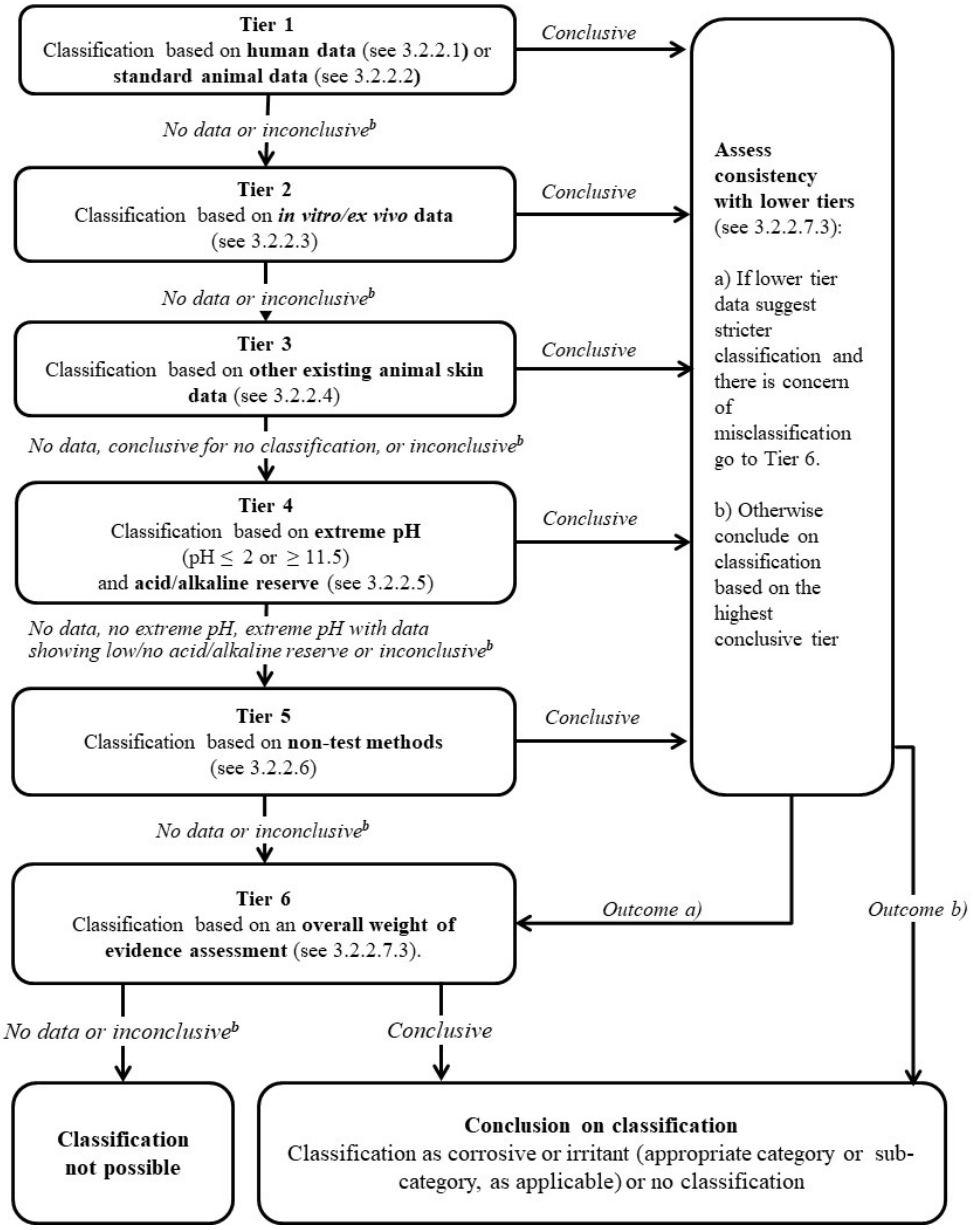
3.2.2.7.1 A tiered approach to the evaluation of initial information should be considered, where applicable (Figure 3.2.1), recognising that not all elements may be relevant. However, all available and relevant information of sufficient quality needs to be examined for consistency with respect to the resulting classification.

3.2.2.7.2 In the tiered approach (Figure 3.2.1), existing human and animal data form the highest tier, followed by *in vitro/ex vivo* data, other existing skin data in animals, and then other sources of information. Where information from data within the same tier is inconsistent and/or conflicting, the conclusion from that tier is determined by a weight of evidence approach.

3.2.2.7.3 Where information from several tiers is inconsistent and/or conflicting with respect to the resulting classification, information of sufficient quality from a higher tier is generally given a higher weight than information from a lower tier. However, when information from a lower tier would result in a stricter classification than information from a higher tier and there is concern for misclassification, then classification is determined by an overall weight of evidence approach. For example, having consulted the guidance in 3.2.5.3 as appropriate, classifiers concerned with a negative result for skin corrosion in an *in vitro/ex vivo* study when there is a positive result for skin corrosion in other

existing skin data in animals would utilise an overall weight of evidence approach. The same would apply in the case where there is human data indicating irritation but positive results from an *in vitro/ex vivo* test for corrosion.

Figure 3.2.1: Application of the tiered approach for skin corrosion and irritation[a]



[a] *Before applying the approach, the explanatory text in 3.2.2.7 as well as the guidance in 3.2.5.3 should be consulted. Only adequate and reliable data of sufficient quality should be included in applying the tiered approach.*

[b] *Information may be inconclusive for various reasons, e.g.:*

- *The available data may be of insufficient quality, or otherwise insufficient/inadequate for the purpose of classification, e.g. due to quality issues related to experimental design and/or reporting;*
- *The available data may be insufficient to conclude on the classification, e.g. they might be adequate to demonstrate irritancy, but inadequate to demonstrate absence of corrosivity;*
- *Where competent authorities make use of the mild skin irritation category 3, the available data may not be capable of distinguishing between category 3 and category 2, or between category 3 and no classification;*
- *The method used to generate the available data may not be suitable for concluding on no classification (see 3.2.2. and 3.2.5.3 for details). Specifically, in vitro/ex vivo and non-test methods need to be validated explicitly for this purpose.*

3.2.3 Classification criteria for mixtures

3.2.3.1 *Classification of mixtures when data are available for the complete mixture*

3.2.3.1.1 In general, the mixture should be classified using the criteria for substances, taking into account the tiered approach to evaluate data for this hazard class (as illustrated in Figure 3.2.1) and 3.2.3.1.2 and 3.2.3.1.3 below. If classification is not possible using the tiered approach, then the approach described in 3.2.3.2 (bridging principles), or, if that is not applicable 3.2.3.3 (calculation method) should be followed.

3.2.3.1.2 *In vitro/ex vivo* data generated from validated test methods may not have been validated using mixtures; although these methods are considered broadly applicable to mixtures, they can only be used for classification of mixtures when all ingredients of the mixture fall within the applicability domain of the test methods used. Specific limitations regarding applicability domains are described in the respective test methods, and should be taken into consideration as well as any further information on such limitations from the published literature. Where there is reason to assume or evidence indicating that the applicability domain of a particular test method is limited, data interpretation should be exercised with caution, or the results should be considered not applicable.

3.2.3.1.3 In the absence of any other information, a mixture is considered corrosive (Skin Category 1) if it has a pH $\leq$ 2 or a pH $\geq$ 11.5. However, if consideration of acid/alkaline reserve suggests the mixture" may not be corrosive despite the low or high pH value, this needs to be confirmed by other data, preferably from an appropriate validated *in vitro/ex vivo* test.

3.2.3.2 *Classification of mixtures when data are not available for the complete mixture: bridging principles*

3.2.3.2.1 Where the mixture itself has not been tested to determine its skin corrosion/ irritation potential, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following agreed bridging principles. This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without the necessity for additional testing in animals.

3.2.3.2.2 *Dilution*

If a tested mixture is diluted with a diluent which has an equivalent or lower skin corrosivity/irritancy classification than the least skin corrosive/irritant original ingredient and which is not expected to affect the skin corrosivity/irritancy of other ingredients, then the new diluted mixture may be classified as equivalent to the original tested mixture. Alternatively, the method explained in 3.2.3.3 could be applied.

3.2.3.2.3 *Batching*

The skin corrosion/irritation potential of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another untested production batch of the same commercial product when produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the skin corrosion/irritation potential of the untested batch has changed. If the latter occurs, a new classification is necessary.

3.2.3.2.4 *Concentration of mixtures of the highest corrosion/irritation category*

If a tested mixture classified in the highest sub-category for skin corrosion is concentrated, the more concentrated untested mixture should be classified in the highest corrosion sub-category without additional testing. If a tested mixture classified for skin irritation (Category 2) is concentrated and does not contain skin corrosive ingredients, the more concentrated untested mixture should be classified for skin irritation (Category 2) without additional testing.

3.2.3.2.5 *Interpolation within one hazard*

For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same skin corrosion/irritation hazard category, and where untested mixture C has the same toxicologically active ingredients as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same skin corrosion/irritation category as A and B.

3.2.3.2.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A + B;
(ii) C + B;

(b) The concentration of ingredient B is essentially the same in both mixtures;

(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);

(d) Data on skin corrosion/irritation for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the skin corrosion/irritation potential of B.

If mixture (i) or (ii) is already classified based on test data, then the other mixture can be classified in the same hazard category.

3.2.3.2.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolized form of the mixture provided that the added propellant does not affect the skin corrosion/irritation properties of the mixture upon spraying.

3.2.3.3 *Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture*

3.2.3.3.1 In order to make use of all available data for purposes of classifying the skin corrosion/irritation hazards of mixtures, the following assumption has been made and is applied where appropriate in the tiered approach:

The "relevant ingredients" of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration < 1% can still be relevant for classifying the mixture for skin corrosion/irritation.

3.2.3.3.2 In general, the approach to classification of mixtures as corrosive or irritant to skin when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each skin corrosive or irritant ingredient contributes to the overall corrosive or irritant properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive ingredients when they are present at a concentration below the concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as corrosive or irritant to skin when the sum of the concentrations of such ingredients exceeds a cut-off value/concentration limit.

3.2.3.3.3 Table 3.2.3 below provides the cut-off value/concentration limits to be used to determine if the mixture is considered to be corrosive or irritant to the skin.

3.2.3.3.4 Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in 3.2.3.3.1 and 3.2.3.3.2 might not work given that many such substances are corrosive or irritant at concentrations < 1%. For mixtures containing strong acids or bases the pH should be used as classification criteria (see 3.2.3.1.2) since pH will be a better indicator of corrosion than the concentration limits in Table 3.2.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach shown in Table 3.2.3, due to chemical characteristics that make this approach unworkable, should be classified as skin corrosion Category 1 if it contains ≥ 1% of a corrosive ingredient and as skin irritation Category 2 or Category 3 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.2.3 does not apply is summarized in Table 3.2.4 below.

3.2.3.3.5 On occasion, reliable data may show that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration limits/cut-off values mentioned in Tables 3.2.3 and 3.2.4. In these cases the mixture could be classified according to those data (see also *Classification of hazardous substances and mixtures – Use of cut-off values/Concentration limits* (1.3.3.2)). On occasion, when it is expected that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off values mentioned in Tables 3.2.3 and 3.2.4, testing of the mixture may be considered. In those cases the tiered weight of evidence approach should be applied as described in 3.2.3 and illustrated in Figure 3.2.1.

3.2.3.3.6 If there are data showing that (an) ingredient(s) may be corrosive or irritant to skin at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly (see also *Classification of hazardous substances and mixtures – Use of cut-off values/Concentration limits* (1.3.3.2)).

Table 3.2.3: Concentration of ingredients of a mixture classified as skin Category 1, 2 or 3 that would trigger classification of the mixture as hazardous to skin (Category 1, 2 or 3)

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:		
	Skin corrosive	Skin irritant	
	Category 1 (see note below)	Category 2	Category 3
Skin Category 1	≥ 5%	≥ 1% but < 5%	
Skin Category 2		≥ 10%	≥ 1% but < 10%
Skin Category 3			≥ 10%
(10 × Skin Category 1) + Skin Category 2		≥ 10%	≥ 1% but < 10%
(10 × Skin Category 1) + Skin Category 2 + Skin Category 3			≥ 10%

NOTE: *Where the sub-categories of skin Category 1 (corrosive) are used, the sum of all ingredients of a mixture classified as sub-category 1A, 1B or 1C respectively, should each be ≥ 5% in order to classify the mixture as either skin sub-category 1A, 1B or 1C. Where the sum of 1A ingredients is < 5% but the sum of 1A+1B ingredients is ≥ 5%, the mixture should be classified as sub-category 1B. Similarly, where the sum of 1A + 1B ingredients is < 5% but the sum of 1A + 1B + 1C ingredients is ≥ 5% the mixture should be classified as sub-category 1C. Where at least one relevant ingredient in a mixture is classified as Category 1 without sub-categorisation, the mixture should be classified as Category 1 without sub-categorisation if the sum of all ingredients corrosive to skin is ≥ 5%.*

Table 3.2.4: Concentration of ingredients of a mixture when the additivity approach does not apply, that would trigger classification of the mixture as hazardous to skin

Ingredient:	Concentration	Mixture classified as: Skin
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11.5	≥ 1%	Category 1
Other corrosive (Category 1) ingredient	≥ 1%	Category 1
Other irritant (Category 2/3) ingredient, including acids and bases	≥ 3%	Category 2/3

3.2.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard communication: Labelling* (Chapter 1.4). Annex 1 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. The table below presents specific label elements for substances and mixtures that are classified as irritating or corrosive to the skin based on the criteria set forth in this chapter.

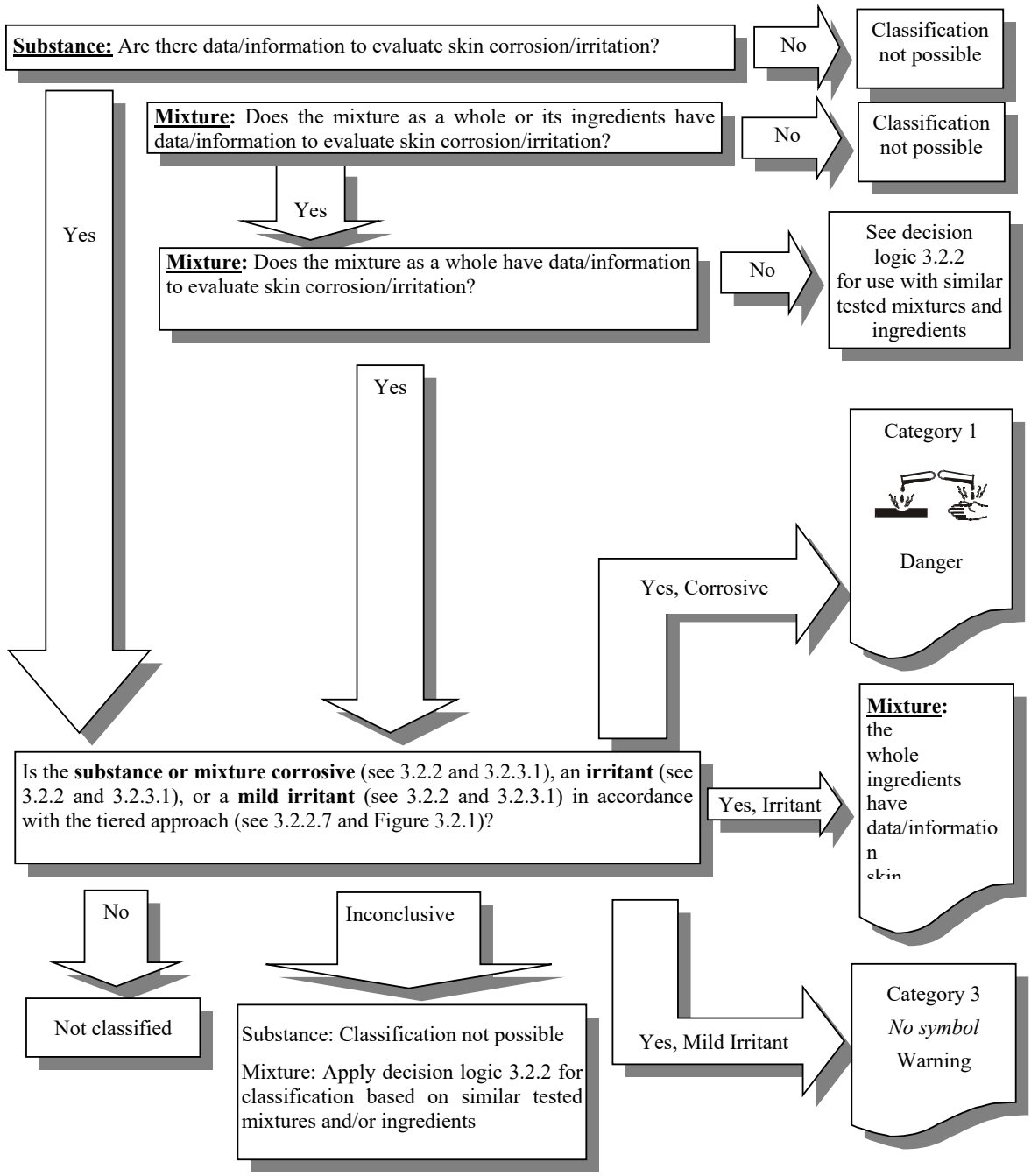
Table 3.2.5: Label elements for skin corrosion/irritation

	Category 1			Category 2	Category 3
	1 A	1 B	1 C		
Symbol	Corrosion	Corrosion	Corrosion	Exclamation mark	*No symbol*
Signal word	Danger	Danger	Danger	Warning	Warning
Hazard statement	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes skin irritation	Causes mild skin irritation

3.2.5 Decision logics and guidance

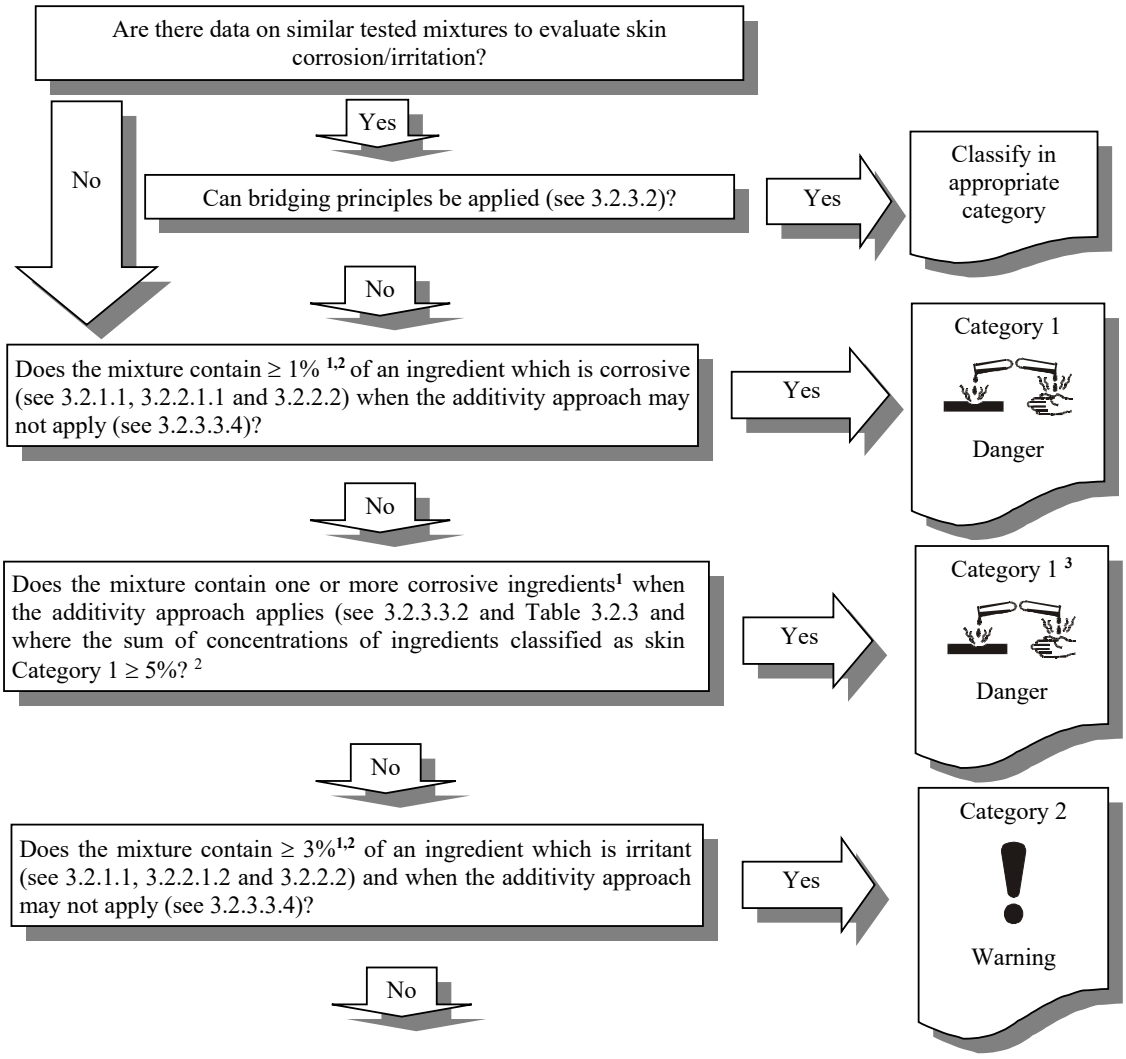
The decision logics which follow are not part of the harmonized classification system but are provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logics.

3.2.5.1 ***Decision logic 3.2.1 for skin corrosion/irritation***



3.2.5.2 ***Decision logic 3.2.2 for skin corrosion/irritation***

Classification of mixtures on the basis of information/data on similar tested mixtures and/or ingredients

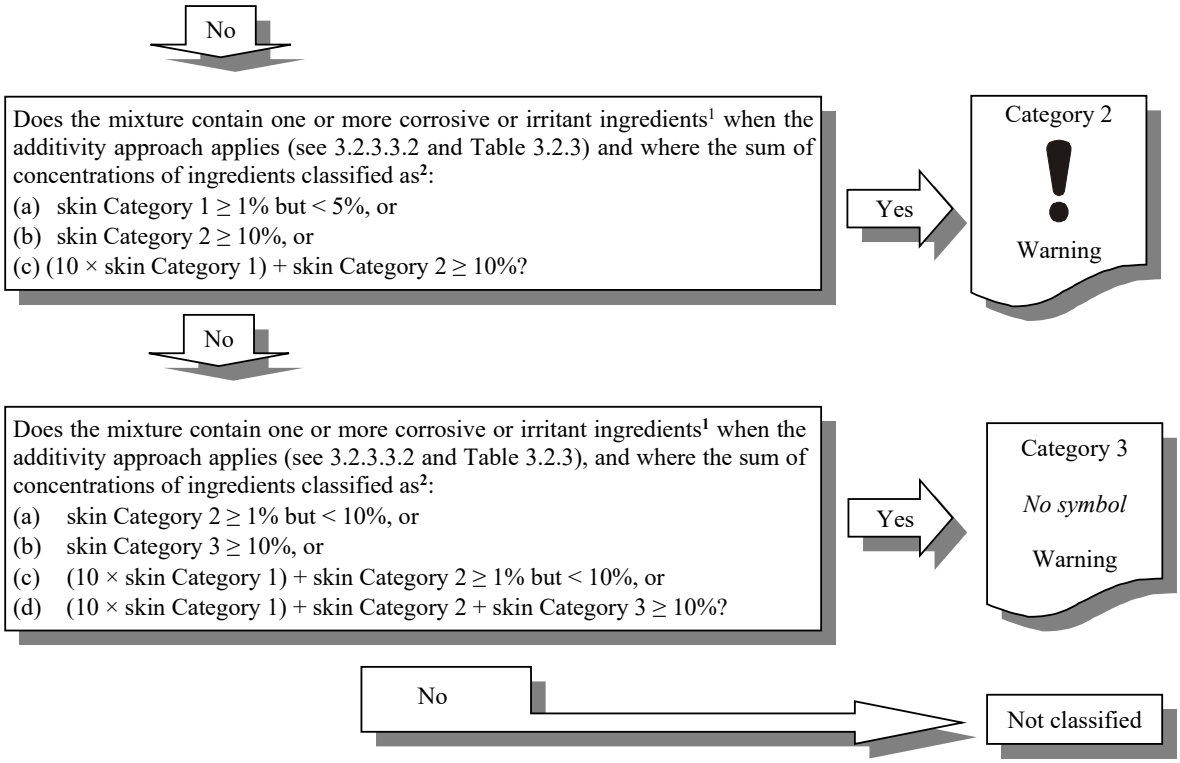


(Cont'd on next page)

[1] *Where relevant < 1%, see 3.2.3.3.1.*

[2] *For specific concentration limits, see 3.2.3.3.6. See also Chapter 1.3, para. 1.3.3.2 for "Use of cut-off values/concentration limits".*

[3] *See note to Table 3.2.3 for details on use of Category 1 sub-categories.*



3.2.5.3 ***Background guidance***

3.2.5.3.1 *Relevant guidance documents*

Helpful information on the strengths and weaknesses of the different test and non-test methods, as well as useful guidance on how to apply a weight of evidence approach, is provided in OECD Guidance document 203 on an integrated approach on testing and assessment (IATA) for skin corrosion and irritation.

3.2.5.3.2 *Guidance on the use of human data for classification as skin corrosion or skin irritation*

3.2.5.3.2.1 Human data generally refers to two types of data: prior human experience (e.g. published case studies from occupational, consumer, transport, emergency response scenarios, epidemiological studies) or from human tests (e.g. clinical trials, dermal patch test). Relevant, reliable and good quality human data is generally given high weight for classification. However, human data may have limitations. Further details on the strengths and limitations of human data for skin irritation/corrosion can be found in OECD Guidance document 203 (section III. A, Part 1, Module 1).

3.2.5.3.2.2 Generally, Human Patch Tests (HPT) are performed to discriminate between irritant and non-irritant substances. Application of a corrosive substance to human skin is generally avoided. Therefore, another test is normally performed in advance to exclude corrosivity. The HPT alone does not normally discriminate between irritant and corrosive substances. In rare circumstances, there may be HPT data that can be used for classification as corrosive (e.g. application of an HPT after a false negative *in vitro* test). However, the combination of an HPT and sufficient other information on skin corrosion can be used for classification within a weight of evidence assessment.

3.2.5.3.2.3 Some competent authorities do not allow HPT testing solely for hazard identification (see 1.3.2.4.7) while some competent authorities recognize the use of HPT for classification as skin irritant.

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[1] *Where relevant < 1%, see 3.2.3.3.1.*

[2] *For specific concentration limits, see 3.2.3.3.6. See also Chapter 1.3, para. 1.3.3.2 for "Use of cut-off values/concentration limits".*

3.2.5.3.2.4 Specific criteria for HPT results leading to classification as category 2 (skin irritation), category 3 (mild irritation) or not classified, have not been established at the international level. Therefore, the results of an HPT are generally used within a weight of evidence assessment. However, some competent authorities may provide specific guidance. A clearly negative result in an HPT with a sufficient number of volunteers after exposure to the undiluted substance for 4 hours can justify no classification.

3.2.5.3.2.5 Human case reports may be used for classification as corrosive if irreversible damage to the skin was observed. There are no internationally accepted classification criteria for irritation. Therefore, where competent authorities have not provided specific guidance on this matter, expert judgement may be required to evaluate whether the exposure duration and any available long-term follow-up information are sufficient to allow for a conclusion on classification. Cases resulting in irritation or no effects may not be conclusive on their own but can be used in a weight of evidence assessment.

3.2.5.3.3 *Classification based on standard animal tests with more than 3 animals*

3.2.5.3.3.1 Classification criteria for the skin and eye hazard classes are detailed in the GHS in terms of a 3-animal test. It has been identified that some older test methods may have used up to 6 animals. However, the GHS criteria do not specify how to classify based on existing data from tests with more than 3 animals. Guidance on how to classify based on existing data from studies with 4 or more animals is given in the following paragraphs.

3.2.5.3.3.2 Classification criteria based on a 3-animal test are detailed in 3.2.2.2. Evaluation of a 4, 5 or 6-animal study should follow the criteria in the following paragraphs, depending on the number of animals tested. Scoring for erythema/eschar and oedema should be performed at 24, 48 and 72 hours after exposure or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions.

3.2.5.3.3.3 In the case of a study with 6 animals the following principles apply:

(a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;

(b) The substance or mixture is classified as skin irritation Category 2 if at least 4 out of 6 animals show a mean score per animal of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema;

(c) The substance or mixture is classified as skin irritation Category 3 if at least 4 out of 6 animals show a mean score per animal of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema.

3.2.5.3.3.4 In the case of a study with 5 animals the following principles apply:

(a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;

(b) The substance or mixture is classified as skin irritation Category 2 if at least 3 out of 5 animals show a mean score per animal of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema;

(c) The substance or mixture is classified as skin irritation Category 3 if at least 3 out of 5 animals show a mean score per animal of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema.

3.2.5.3.3.5 In the case of a study with 4 animals the following principles apply:

(a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;

(b) The substance or mixture is classified as skin irritation Category 2 if at least 3 out of 4 animals show a mean score per animal of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema;

(c) The substance or mixture is classified as skin irritation Category 3 if at least 3 out of 4 animals show a mean score per animal of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema.

3.2.5.3.4 *Classification criteria based on in-vitro/ex vivo data*

Where *in vitro/ex vivo* tests have been undertaken in accordance with OECD Test Guidelines 430, 431, 435 or 439, the criteria for classification in category 1 (and, where possible and required into sub-categories 1A, 1B or 1C) for skin corrosion and in category 2 for skin irritation are set out in Tables 3.2.6 and 3.2.7.

Table 3.2.6: Skin corrosion criteria for *in vitro/ex vivo* methods

Category	OECD Test Guideline 430 (Transcutaneous Electrical Resistance test method)	OECD Test Guideline 431 Reconstructed human Epidermis test methods: Methods 1, 2, 3, 4 as numbered in Annex 2 of OECD Test Guideline 431				OECD Test Guideline 435 Membrane barrier test method	
	Using rat skin discs corrosive chemicals are identified by their ability to produce a loss of normal *stratum corneum* integrity. Barrier function of the skin is assessed by recording the passage of ions through the skin. The electrical impedance of the skin is measured using transcutaneous electrical resistance (TER). A confirmatory test of positive results using a dye-binding step that assesses if an increase in ionic permeability is due to the physical destruction of the *stratum corneum* is performed in case of a reduced TER (less than or around 5 kΩ) in the absence of obvious damage. The criteria are based on the mean TER value in kΩ and sometimes on dye content.	Four similar methods where the test chemical is applied topically to a three-dimensional reconstructed human epidermis (RhE) which closely mimics the properties of the upper parts of human skin. The test method is based on the premise that corrosive chemicals are able to penetrate the *stratum corneum* by diffusion or erosion, and are cytotoxic to the cells in the underlying layers. Tissue viability is assessed by enzymatic conversion of the dye MTT into a blue formazan salt that is quantitatively measured after extraction from the tissues. Corrosive chemicals are identified by their ability to decrease tissue viability below defined threshold values. The criteria are based on the percent tissue viability following a defined exposure period.				An *in vitro* membrane barrier test method comprising a synthetic macromolecular bio-barrier and a chemical detection system (CDS). Barrier damage is measured after the application of the test chemical to the surface of the synthetic membrane barrier. The criteria are based on the mean penetration/breakthrough time of the chemical through the membrane barrier.	
						Type 1 chemicals (high acid/alkaline reserve)	Type 2 chemicals (low acid/alkaline reserve)
1	(a) mean TER value ≤ 5 kΩ and the skin discs are obviously damaged (e.g. perforated), or (b) mean TER value ≤ 5 kΩ, and (i) the skin discs show no obvious damage (e.g. perforation), but (ii) the subsequent confirmatory testing of positive results using a dye binding step is positive.	Method 1 < 35% after 3, 60 or 240 min exposure	Methods 2, 3, 4 < 50% after 3 min exposure; or ≥ 50% after 3 min exposure and < 15% after 60 min exposure			≤ 240 min	≤ 60 min
1A	Not applicable	Method 1 < 35% after 3 min exposure	Method 2 < 25% after 3 min exposure	Method 3 < 18% after 3 min exposure	Method 4 < 15% after 3 min exposure	0-3 min.	0-3 min
1B		≥ 35% after 3 min exposure and < 35% after 60 min exposure or ≥ 35% after 60 min exposure and < 35% after 240 min exposure	≥ 25% after 3 min exposure and fulfilling criteria for category 1	≥ 18% after 3 min exposure and fulfilling criteria for category 1	≥ 15% after 3 min exposure and fulfilling criteria for category 1	> 3 to 60 min.	> 3 to 30 min
1C						> 60 to 240 min.	> 30 to 60 min
Not classified as skin corrosive	(a) the mean TER value > 5 kΩ, or (b) the mean TER value ≤ 5 kΩ, and (i) the skin discs show no obvious damage (e.g. perforation), and (ii) the subsequent confirmatory testing of positive results using a dye binding step is negative	≥ 35% after 240 min exposure	≥ 50% after 3 min exposure and ≥ 15% after 60 min exposure			> 240 min.	> 60 min

Table 3.2.7 Skin irritation criteria for *in vitro* methods

Category	**Test Guideline 439** **Reconstructed Human Epidermis test methods**
	Four similar methods (1-4) where the test chemical is applied topically to a three-dimensional reconstructed human epidermis (RhE) which closely mimics the properties of the upper parts of human skin. Tissue viability is assessed by enzymatic conversion of the dye MTT into a blue formazan salt that is quantitatively measured after extraction from the tissues. Positive chemicals are identified by their ability to decrease tissue viability below defined threshold levels. The criteria are based on mean percent tissue viability after exposure and post-treatment incubation.
1 or 2	Mean percent tissue viability (≤) 50%. Note: The RhE test methods covered by this Test Guideline cannot resolve between GHS categories 1 and 2. Further information on skin corrosion will be required to decide on its final classification [see also the OECD Guidance document 203].
2	Mean percent tissue viability ≤ 50% and the test chemical is found to be noncorrosive (e.g., based on TG 430, 431 or 435)
Not classified as skin irritant or category 3	Mean percent-tissue viability > 50% Note: The RhE test methods covered by this TG cannot resolve between GHS optional category 3 and not classified as skin irritant. Further information on skin irritation is required for those authorities that want to have more than one skin irritation category.

3.2.5.3.5 *Guidance on the use of other existing skin data in animals for classification as skin corrosion or skin irritation*

3.2.5.3.5.1 General approach

All existing other animal data should be carefully reviewed and only used if they are conclusive for classification. In evaluating other existing skin data in animals, however, it should be recognised that the reporting of dermal lesions may be incomplete, testing and observations may be made in a species other than the rabbit, and species may differ in sensitivity in their responses. In general skin thickness decreases with body weight. However, other factors also affect species variability. In addition, for most of these tests, irritating and corrosive effects need to be avoided. Therefore, these effects may only be observed in range finding studies using a small number of animals with limited observations and reporting.

3.2.5.3.5.2 Other data limitations and consequences for classification

3.2.5.3.5.2.1 Acute dermal toxicity tests, repeated dose animal studies, skin sensitisation studies and skin absorption studies may all differ from the standard in vivo acute dermal irritation/corrosion test (e.g. OECD Test Guideline 404) with regard to exposure duration, area dose, the use of dissolved substances, level of occlusion, patch type, scoring and follow-up of the skin lesions and the test species.

3.2.5.3.5.2.2 Destruction of the skin in any acute dermal toxicity test (e.g. OECD Test Guideline 402) should be considered for classification as corrosive (category 1 or sub-category 1A, 1B or 1C where possible and required). Skin irritation in an acute dermal study in rabbits fulfilling the criteria in Table 3.2.2, should be considered for classification as irritant if the exposure conditions are such that corrosive effects can be excluded. Skin irritation in an acute dermal study in other species should be considered as not conclusive, as these species may be less or more sensitive than rabbits. Such data should be taken into account in a weight-of-evidence assessment. The absence of skin irritation should also be considered as not conclusive and taken into account in a weight-of-evidence assessment.

3.2.5.3.5.2.3 Repeated dose dermal studies (e.g. OECD Test Guidelines 410 and 412) can be used to classify as corrosive when destruction of the skin is observed after the initial exposures. However, normally such exposures are avoided and corrosive effects may only be observed in the range-finding studies. Moreover, sub-categorisation for corrosion will rarely be possible due to a longer time period between start of exposure and first observation. The observation of skin irritation or the absence of skin irritating effects should be considered as not conclusive. Skin effects only observed after multiple exposures may indicate skin sensitisation rather than skin irritation.

3.2.5.3.5.2.4 In skin sensitisation studies in guinea pigs (e.g. OECD Test Guideline 406), severely irritating and corrosive exposure must be avoided. Therefore, such effects are normally only observed in range-finding studies. The range-finding results, with the exception of intradermal exposure in the maximisation test, can be used to classify as corrosive when destruction of the skin is observed. The presence or absence of skin irritation in a skin sensitisation study should be considered as not conclusive by itself as the species tested may be more or less sensitive than rabbits, but signs of irritation should be taken into account in a weight of evidence assessment.

3.2.5.3.5.2.5 Irritation data from the Local Lymph Node Assay (e.g. OECD Test Guidelines 429, 442A and 442B) should normally not be used for classification as the test substance is applied to the dorsum of the ear by open topical application, and in some cases specific vehicles for enhancement of skin penetration are used. Further, due to the proportional increase of skin thickness associated with increased body weight, the skin thickness of mice deviates significantly from that of rabbits and humans.

3.2.5.3.5.2.6 In skin absorption studies (e.g. OECD Test Guideline 427), corrosive exposure conditions are generally avoided as this affects the absorption. Therefore, information on skin effects from these studies does not allow classification directly but may be considered within a weight of evidence approach. However, information on the dermal absorption may be taken into account in a weight-of-evidence assessment as a high dermal absorption in combination with additional evidence for high cytotoxicity may indicate irritation or corrosivity.

CHAPTER 3.3

SERIOUS EYE DAMAGE/EYE IRRITATION

3.3.1 Definitions and general considerations

3.3.1.1 *Serious eye damage* refers to the production of tissue damage in the eye, or serious physical decay of vision, which is not fully reversible, occurring after exposure of the eye to a substance or mixture.

Eye irritation refers to the production of changes in the eye, which are fully reversible, occurring after the exposure of the eye to a substance or mixture.

3.3.1.2 In a tiered approach, emphasis should be placed upon existing human data, followed by existing animal data, followed by *in vitro* data and then other sources of information. Classification results directly when the data satisfy the criteria. In other cases, classification of a substance or a mixture is made on the basis of the weight of evidence within a tier. In a total weight of evidence approach all available information bearing on the determination of serious eye damage/eye irritation is considered together, including the results of appropriate validated *in vitro* tests, relevant animal data, and human data such as epidemiological and clinical studies and well-documented case reports and observations (see Chapter 1.3, para. 1.3.2.4.9).

3.3.2 Classification criteria for substances

Substances are allocated to one of the categories within this hazard class, Category 1 (serious eye damage) or Category 2 (eye irritation), as follows:

(a) Category 1 (serious eye damage/irreversible effects on the eye):

substances that have the potential to seriously damage the eyes (see Table 3.3.1).

(b) Category 2 (eye irritation/reversible effects on the eye):

substances that have the potential to induce reversible eye irritation (see Table 3.3.2).

Those authorities desiring one category for classification of "eye irritation" may use the overall Category 2; others may want to distinguish between Category 2A and Category 2B (see Table 3.3.2).

3.3.2.1 *Classification based on standard animal test data*

3.3.2.1.1 *Serious eye damage (Category 1)/irreversible effects on the eye*

A single hazard category (Category 1) is adopted for substances that have the potential to seriously damage the eyes. This hazard category includes as criteria the observations listed in Table 3.3.1. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g. destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those which are not fully reversible within an observation period of normally 21 days. Hazard classification as Category 1 also contains substances fulfilling the criteria of corneal opacity ≥ 3 or iritis > 1.5 observed in at least 2 of 3 tested animals, because severe lesions like these usually do not reverse within a 21 days observation period.

Table 3.3.1: Serious eye damage/Irreversible effects on the eye category[a, b, c]

	Criteria
Category 1: **Serious eye damage/Irreversible effects on the eye**	A substance that produces: (a) in at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or (b) in at least 2 of 3 tested animals, a positive response of: (i) corneal opacity ≥ 3; and/or (ii) iritis > 1.5; calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material.

[a] *The use of human data is addressed in 3.3.2.2 and in chapters 1.1 (para. 1.1.2.5 (c)) and 1.3 (para. 1.3.2.4.7).*

[b] *Grading criteria are understood as described in OECD Test Guideline 405.*

[c] *Evaluation of a 4, 5 or 6-animal study should follow the criteria given in 3.3.5.3.*

3.3.2.1.2 *Eye irritation (Category 2)/Reversible effects on the eye*

3.3.2.1.2.1 Substances that have the potential to induce reversible eye irritation should be classified in Category 2 where further categorization into Category 2A and Category 2B is not required by a competent authority or where data are not sufficient for further categorization. When a chemical is classified as Category 2, without further categorization, the classification criteria are the same as those for Category 2A.

3.3.2.1.2.2 For those authorities wanting more than one designation for reversible eye irritation, categories 2A and 2B are provided:

(a) When data are sufficient and where required by a competent authority substances may be classified in Category 2A or 2B in accordance with the criteria in Table 3.3.2;

(b) For substances inducing eye irritant effects reversing within an observation time of normally 21 days, Category 2A applies. For substances inducing eye irritant effects reversing within an observation time of 7 days, Category 2B applies.

3.3.2.1.2.3 For those substances where there is pronounced variability among animal responses, this information may be taken into account in determining the classification.

Table 3.3.2: Reversible effects on the eye categories [a, b, c]

	Criteria
	Substances that have the potential to induce reversible eye irritation
Category 2/2A	Substances that produce in at least 2 of 3 tested animals a positive response of: (a) corneal opacity ≥ 1; and/or (b) iritis ≥ 1; and/or (c) conjunctival redness ≥ 2; and/or (d) conjunctival oedema (chemosis) ≥ 2 calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material, and which fully reverses within an observation period of normally 21 days.
Category 2B	Within Category 2A an eye irritant is considered mildly irritating to eyes (Category 2B) when the effects listed above are fully reversible within 7 days of observation.

[a] *The use of human data is addressed in 3.3.2.2 and in chapters 1.1 (para. 1.1.2.5(c)), and 1.3 (para. 1.3.2.4.7).*

[b] *Grading criteria are understood as described in OECD Test Guideline 405.*

[c] *Evaluation of a 4, 5 or 6-animal study should follow the criteria given in 3.3.5.3.*

3.3.2.2 *Classification in a tiered approach*

3.3.2.2.1 A tiered approach to the evaluation of initial information should be considered where applicable (Figure 3.3.1), recognizing that not all elements may be relevant.

3.3.2.2.2 Existing human and animal data should be the first line of evaluation as they give information directly relevant to effects on the eye. Possible skin corrosion has to be evaluated prior to consideration of any testing for serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances.

3.3.2.2.3 *In vitro* alternatives that have been validated and accepted should be used to make classification decisions.

3.3.2.2.4 Likewise, pH extremes like ≤ 2 and ≥ 11.5, may indicate serious eye damage, especially when associated with significant acid/alkaline reserve (buffering capacity). Generally such substances are expected to produce significant effects on the eyes. In the absence of any other information, a substance is considered to cause serious eye damage (Category 1) if it has a pH ≤ 2 or ≥ 11.5. However, if consideration of acid/alkaline reserve suggests the substance may not cause serious eye damage despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated *in vitro* test.

3.3.2.2.5 In some cases sufficient information may be available from structurally related substances to make classification decisions.

3.3.2.2.6 The tiered approach provides guidance on how to organize existing information and to make a weight-of-evidence decision about hazard assessment and hazard classification (ideally without conducting new animal tests). Animal testing with corrosive substances should be avoided whenever possible. Although information might be gained from the evaluation of single parameters within a tier (see 3.3.2.1.1) consideration should be given to the totality of existing information and making an overall weight of evidence determination. This is especially true when there is conflict in information available on some parameters.

Figure 3.3.1: Tiered evaluation for serious eye damage/eye irritation (see also Figure 3.2.1)

Step	Parameter	Finding	Conclusion
1a:	Existing human or animal serious eye damage/eye irritation data [a] →	Serious eye damage →	Classify as causing **serious eye damage**
	↓ ↘	Eye irritant →	Classify as **eye irritant** [b]
	Negative data/Insufficient data/No data ↓		
1b:	Existing human or animal data, skin corrosion →	Skin corrosion →	Deemed to cause **serious eye damage**
	↓		
	Negative data/Insufficient data/No data ↓		
1c:	Existing human or animal serious eye damage/eye irritation data [a] →	Existing data showing that substance does not cause serious eye damage or eye irritation →	**Not classified**
	↓		
	No/Insufficient data ↓		
2:	Other, existing skin/eye data in animals [c] →	Yes; other existing data showing that substance may cause serious eye damage or eye irritation →	May be deemed to cause **serious eye damage** or to be an **eye irritant** [b]
	↓		
	No/Insufficient data ↓		
3:	Existing *ex vivo/in vitro eye* data[d] →	Positive: serious eye damage →	Classify as causing **serious eye damage**
	↓ ↘	Positive: eye irritant →	Classify as **eye irritant** [b]
	No/Insufficient data/Negative response ↓		
4:	pH-based assessment (with consideration of acid/alkaline reserve of the chemical) [e] →	pH ≤ 2 or ≥ 11.5 with high acid/alkaline reserve or no data for acid/alkaline reserve →	Classify as causing **serious eye damage**
	↓		
	Not pH extreme, no pH data or extreme pH with data showing low/no acid/alkaline reserve ↓		
5:	↗	Severe damage to eyes →	Deemed to cause **serious eye damage**
	Validated Structure Activity Relationship (SAR) methods →	Eye irritant →	Deemed to be **eye irritant** [b]
	↓ ↘	Skin corrosive →	Deemed to cause **serious eye damage**
	No/Insufficient data ↓		
6:	Consideration of the total weight of evidence [f] →	Serious eye damage →	Deemed to cause **serious eye damage**
	↓ ↘	Eye irritant →	Deemed to be **eye irritant** [b]
7:	**Not classified**		

(a) Existing human or animal data could be derived from single or repeated exposure(s), for example in occupational, consumer, transport, or emergency response scenarios; or from purposely-generated data from animal studies conducted according to validated and internationally accepted test methods. Although human data from accident or poison centre databases can provide evidence for classification, absence of incidents is not itself evidence for no classification as exposures are generally unknown or uncertain;

(b) Classify in the appropriate category as applicable;

(c) Existing animal data should be carefully reviewed to determine if sufficient serious eye damage/eye irritation evidence is available through other, similar information. It is recognized that not all skin irritants are eye irritants. Expert judgment should be exercised prior to making such a determination;

(d) Evidence from studies using validated protocols with isolated human/animal tissues or other non-tissue-based, validated protocols should be assessed. Examples of internationally accepted, validated test methods for identifying eye corrosives and severe irritants (i.e., Serious Eye Damage) include OECD Test Guidelines 437 (Bovine Corneal Opacity and Permeability (BCOP)), 438 (Isolated Chicken Eye (ICE) and 460 (Fluorescein leakage (FL)). Presently there are no validated and internationally accepted in vitro test methods for identifying eye irritation. A positive test result from a validated in vitro test on skin corrosion would lead to the conclusion to classify as causing serious eye damage;

(e) Measurement of pH alone may be adequate, but assessment of acid/alkaline reserve (buffering capacity) would be preferable. Presently, there is no validated and internationally accepted method for assessing this parameter;

(f) All information that is available on a substance should be considered and an overall determination made on the total weight of evidence. This is especially true when there is conflict in information available on some parameters. The weight of evidence including information on skin irritation may lead to classification for eye irritation. Negative results from applicable validated in vitro tests are considered in the total weight of evidence evaluation.

3.3.3 Classification criteria for mixtures

3.3.3.1 *Classification of mixtures when data are available for the complete mixture*

3.3.3.1.1 The mixture should be classified using the criteria for substances, and taking into account the tiered approach to evaluate data for this hazard class (as illustrated in Figure 3.3.1).

3.3.3.1.2 When considering testing of the mixture, classifiers are encouraged to use a tiered weight of evidence approach as included in the criteria for classification of substances for skin corrosion and serious eye damage and eye irritation to help ensure an accurate classification, as well as to avoid unnecessary animal testing. In the absence of any other information, a mixture is considered to cause serious eye damage (Eye Category 1) if it has a pH ≤ 2 or ≥ 11.5. However, if consideration of alkali/acid reserve suggests the mixture may not cause serious eye damage despite the low or high pH value this needs to be confirmed by other data, preferably data from an appropriate validated *in vitro* test.

3.3.3.2 *Classification of mixtures when data are not available for the complete mixture: bridging principles*

3.3.3.2.1 Where the mixture itself has not been tested to determine its skin corrosivity or potential to cause serious eye damage or eye irritation, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following agreed bridging principles. This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without the necessity for additional testing in animals.

3.3.3.2.2 *Dilution*

If a tested mixture is diluted with a diluent which has an equivalent or lower classification for serious eye damage/eye irritation than the least seriously eye damaging/eye irritant original ingredient and which is not expected to affect the serious eye damage /eye irritancy of other ingredients, then the new diluted mixture may be classified as equivalent to the original tested mixture. Alternatively, the method explained in 3.3.3.3 could be applied.

3.3.3.2.3 *Batching*

The serious eye damage/eye irritation potential of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another untested production batch of the same commercial product when produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the serious eye damage/eye irritation potential of the untested batch has changed. If the latter occurs, a new classification is necessary.

3.3.3.2.4 *Concentration of mixtures of the highest serious eye damage/eye irritation category*

If a tested mixture classified for serious eye damage (Category 1) is concentrated, the more concentrated untested mixture should be classified for serious eye damage (Category 1) without additional testing. If a tested mixture classified for eye irritation (Category 2 or 2A) is concentrated and does not contain serious eye damage ingredients, the more concentrated untested mixture should be classified in the same category (Category 2 or 2A) without additional testing.

3.3.3.2.5 *Interpolation within one hazard category*

For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same serious eye damage/eye irritation hazard category, and where untested mixture C has the same toxicologically active ingredients as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same serious eye damage/eye irritation category as A and B.

3.3.3.2.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A +B
(ii) C + B;

(b) The concentration of ingredient B is essentially the same in both mixtures;

(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);

(d) Data on serious eye damage/eye irritation for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the serious eye damage/eye irritation potential of B.

If mixture (i) or (ii) is already classified by testing, the other mixture can be assigned in the same hazard category.

3.3.3.2.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolized form of mixture provided that the added propellant does not affect the serious eye damage/eye irritation properties of the mixture upon spraying[1].

3.3.3.3 *Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture*

3.3.3.3.1 In order to make use of all available data for purposes of classifying the serious eye damage/eye irritation properties of the mixtures, the following assumption has been made and is applied where appropriate in the tiered approach:

The "relevant ingredients" of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration < 1% can still be relevant for classifying the mixture for serious eye damage/eye irritation.

[1] *Bridging principles apply for the intrinsic hazard classification of aerosols, however, the need to evaluate the potential for "mechanical" eye damage from the physical force of the spray is recognized.*

3.3.3.3.2 In general, the approach to classification of mixtures as seriously damaging to the eye or eye irritant when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or serious eye damaging/eye irritant ingredient contributes to the overall serious eye damage/eye irritation properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive and serious eye damaging ingredients when they are present at a concentration below the concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as serious eye damaging/eye irritant. The mixture is classified as seriously damaging to the eye or eye irritant when the sum of the concentrations of such ingredients exceeds a threshold cut-off value/concentration limit.

3.3.3.3.3 Table 3.3.3 provides the cut-off value/concentration limits to be used to determine if the mixture should be classified as seriously damaging to the eye or an eye irritant.

3.3.3.3.4 Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in 3.3.3.3.1 and 3.3.3.3.2 might not work given that many such substances are seriously damaging to the eye/eye irritating at concentrations < 1%. For mixtures containing strong acids or bases the pH should be used as classification criterion (see 3.3.3.1.2) since pH will be a better indicator of serious eye damage (subject to consideration of acid/alkali reserve) than the concentration limits in Table 3.3.3. A mixture containing corrosive or serious eye damaging/eye irritating ingredients that cannot be classified based on the additivity approach applied in Table 3.3.3 due to chemical characteristics that make this approach unworkable, should be classified as Eye Category 1 if it contains ≥ 1% of a corrosive or serious eye damaging ingredient and as Eye Category 2 when it contains ≥ 3% of an eye irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.3.3 does not apply is summarized in Table 3.3.4.

3.3.3.3.5 On occasion, reliable data may show that the irreversible/reversible eye effects of an ingredient will not be evident when present at a level above the generic cut-off values/concentration limits mentioned in Tables 3.3.3 and 3.3.4. In these cases the mixture could be classified according to those data (see also 1.3.3.2 *"Use of cut-off values/Concentration limits"*). On occasion, when it is expected that the skin corrosion/irritation or the irreversible/reversible eye effects of an ingredient will not be evident when present at a level above the generic concentration/cut-off levels mentioned in Tables 3.3.3 and 3.3.4, testing of the mixture may be considered. In those cases, the tiered weight of evidence approach should be applied as referred to in section 3.3.3, Figure 3.3.1 and explained in detail in this chapter.

3.3.3.3.6 If there are data showing that (an) ingredient(s) may be corrosive to the skin or seriously damaging to the eye/eye irritating at a concentration of < 1% (corrosive to the skin or seriously damaging to the eye) or < 3% (eye irritant), the mixture should be classified accordingly (see also 1.3.3.2 *"Use of cut-off values/concentration limits"*).

Table 3.3.3: Concentration of ingredients of a mixture classified as skin Category 1 and/or eye Category 1 or 2 that would trigger classification of the mixture as hazardous to the eye (Category 1 or 2)

Sum of ingredients classified as	**Concentration triggering classification of a mixture as**	
	Serious eye damage	**Eye irritation**
	Category 1	**Category 2/2A**
Skin Category 1 + Eye Category 1[a]	≥ 3%	≥ 1% but < 3%
Eye Category 2		≥ 10% [b]
10 × (skin Category 1 + eye Category 1)[a] + eye Category 2		≥ 10%

[a] *If an ingredient is classified as both skin Category 1 and eye Category 1 its concentration is considered only once in the calculation;*

[b] *A mixture may be classified as eye Category 2B when all relevant ingredients are classified as eye Category 2B.*

Table 3.3.4: Concentration of ingredients of a mixture when the additivity approach does not apply, that would trigger classification of the mixture as hazardous to the eye

Ingredient	**Concentration**	**Mixture classified as: Eye**
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11.5	≥ 1%	Category 1
Other corrosive (eye Category 1) ingredient	≥ 1%	Category 1
Other eye irritant (eye Category 2) ingredient	≥ 3%	Category 2

3.3.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard communication: Labelling* (Chapter 1.4). Annex 1 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 3.3.5: Label elements for serious eye damage/eye irritation [a]

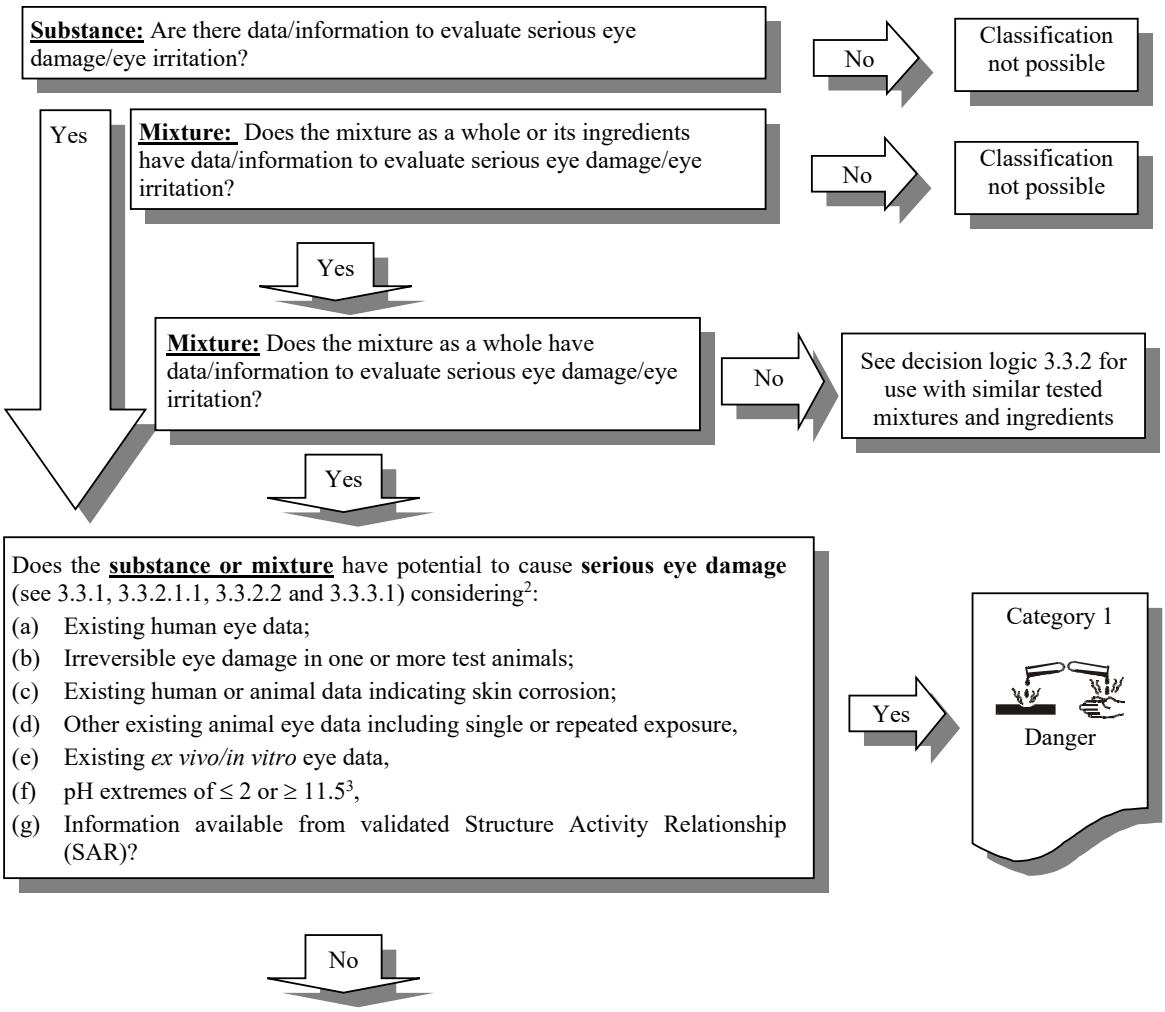
	Category 1	Category 2A	Category 2B
Symbol	Corrosion	Exclamation mark	*No symbol*
Signal word	Danger	Warning	Warning
Hazard statement	Causes serious eye damage	Causes serious eye irritation	Causes eye irritation

[a] *Where a chemical is classified as skin Category 1, labelling for serious eye damage/eye irritation may be omitted as this information is already included in the hazard statement for skin Category 1 (Causes severe skin burns and eye damage) (see Chapter 1.4, para. 1.4.10.5.3.3).*

3.3.5 Decision logics and guidance

The decision logics which follow are not part of the harmonized classification system but are provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logics.

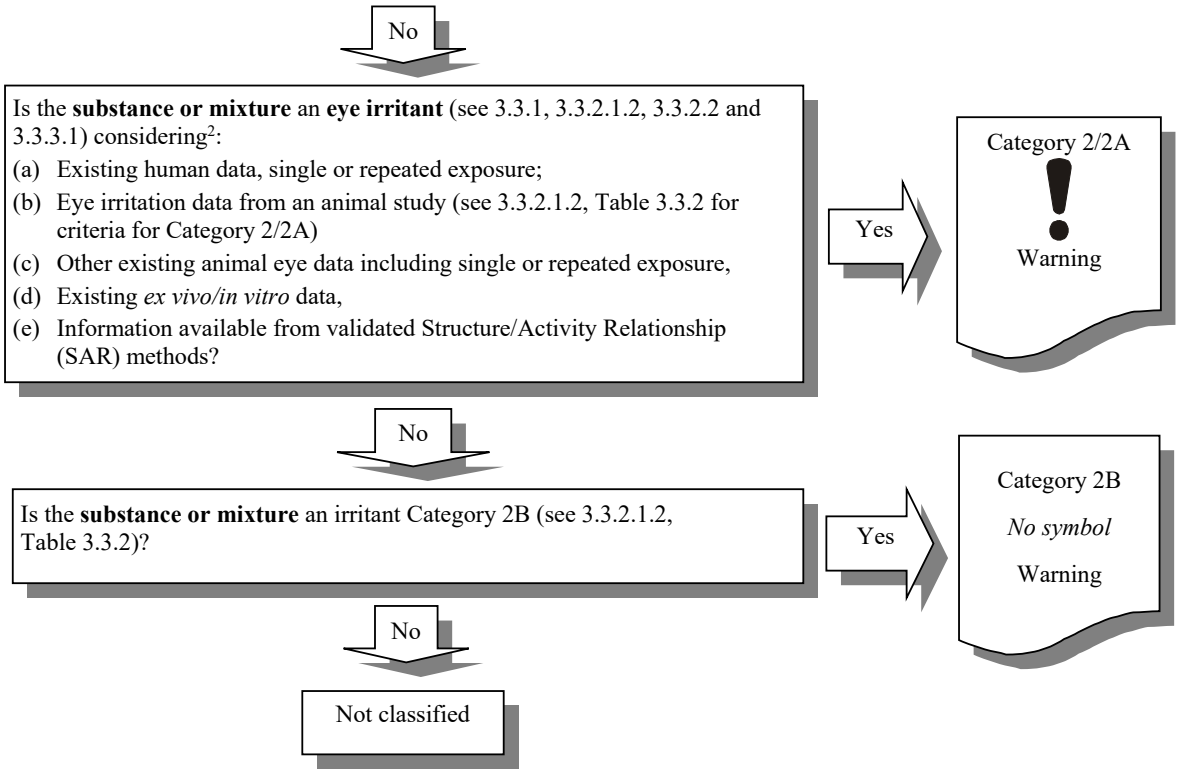
3.3.5.1 *Decision logic 3.3.1 for serious eye damage/eye irritation*



(Cont'd on next page)

[2] *Taking into account consideration of the total weight of evidence as needed.*

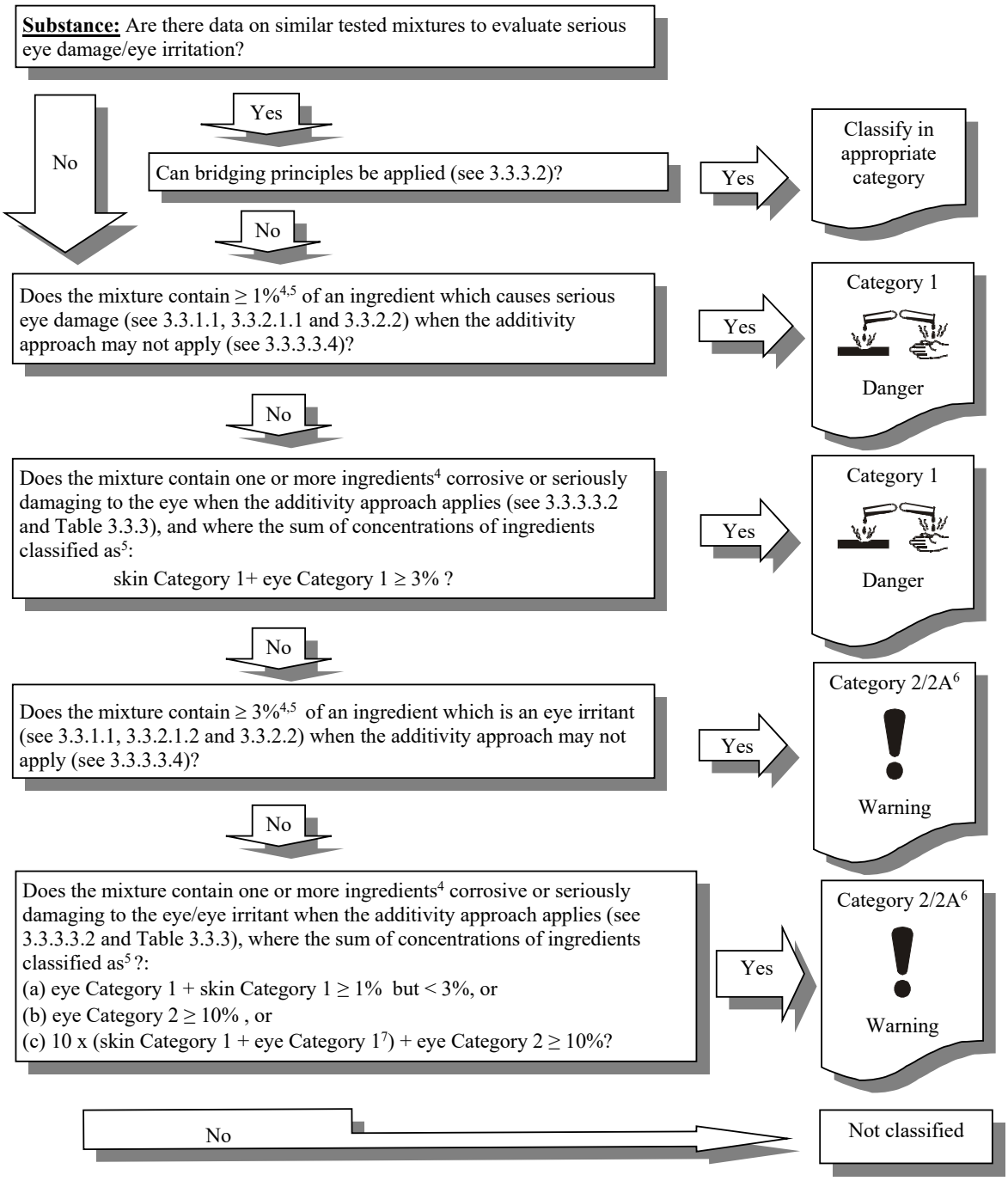
[3] *Not applicable if consideration of pH and acid/alkaline reserve indicates the substance or mixture many not cause serious eye damage and confirmed by other data, preferably by data from an appropriate validated in vitro test.*



[2] *Taking into account consideration of the total weight of evidence as needed.*

3.3.5.2 Decision logic 3.3.2 for serious eye damage/eye irritation

Classification of mixtures on the basis of information/data on similar tested mixtures and ingredients



[4] *Where relevant < 1%, see 3.3.3.3.1.*

[5] *For specific concentration limits, see 3.3.3.3.5 and 3.3.3.3.6. See also Chapter 1.3, para. 1.3.3.2 "Use of cut-off values/concentration limits".*

[6] *A mixture may be classified as eye Category 2B in case all relevant ingredients are classified as eye Category 2B.*

[7] *If an ingredient is classified as both skin Category 1 and eye Category 1 its concentration is considered only once in the calculation.*

3.3.5.3 ***Background guidance***

3.3.5.3.1 Classification criteria for the skin and eye hazard classes are detailed in the GHS in terms of a 3-animal test. It has been identified that some older test methods may have used up to 6 animals. However, the GHS criteria do not specify how to classify based on existing data from tests with more than 3 animals. Guidance on how to classify based on existing data from studies with 4 or more animals is given in the following paragraphs.

3.3.5.3.2 Classification criteria based on a 3-animal test are detailed in 3.3.2.1. Evaluation of a 4, 5 or 6 animal study should follow the criteria in the following paragraphs, depending on the number of animals tested. Scoring should be done at 24, 48 and 72 hours after instillation of the test material.

3.3.5.3.3 In the case of a study with 6 animals the following principles apply:

(a) The substance or mixture is classified as serious eye damage Category 1 if:

(i) at least in one animal effects on the cornea, iris or conjunctiva are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or

(ii) at least 4 out of 6 animals show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis.

(b) The substance or mixture is classified as eye irritation Category 2/2A if at least 4 out of 6 animals show a mean score per animal of:

(i) ≥ 1 for corneal opacity; and/or

(ii) ≥ 1 for iritis; and/or

(iii) ≥ 2 for conjunctival redness; and/or

(iv) ≥ 2 for conjunctival oedema (chemosis),

and which fully reverses within an observation period of normally 21 days.

(c) The substance or mixture is classified as irritating to eyes (Category 2B) if the effects listed in sub-paragraph (b) above are fully reversible within 7 days of observation.

3.3.5.3.4 In the case of a study with 5 animals the following principles apply:

(a) The substance or mixture is classified as serious eye damage Category 1 if:

(i) at least in one animal effects on the cornea, iris or conjunctiva are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or

(ii) at least 3 out of 5 animals show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis.

(b) The substance or mixture is classified as eye irritation Category 2/2A if at least 3 out of 5 animals show a mean score per animal of:

(i) ≥ 1 for corneal opacity; and/or

(ii) ≥ 1 for iritis; and/or

(iii) ≥ 2 for conjunctival redness; and/or

(iv) ≥ 2 for conjunctival oedema (chemosis),

and which fully reverses within an observation period of normally 21 days.

(c) The substance or mixture is classified as irritating to eyes (Category 2B) if the effects listed in sub-paragraph (b) above are fully reversible within 7 days of observation.

3.3.5.3.5 In the case of a study with 4 animals the following principles apply:

(a) The substance or mixture is classified as serious eye damage Category 1 if:

(i) at least in one animal effects on the cornea, iris or conjunctiva are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or

(ii) at least 3 out of 4 animals show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis.

(b) Classification as eye irritation Category 2/2A if at least 3 out of 4 animals show a mean score per animal of:

(i) ≥ 1 for corneal opacity; and/or

(ii) ≥ 1 for iritis; and/or

(iii) ≥ 2 for conjunctival redness; and/or

(iv) ≥ 2 for conjunctival oedema (chemosis),

and which fully reverses within an observation period of normally 21 days.

(c) The substance or mixture is classified as irritating to eyes (Category 2B) if the effects listed in sub-paragraph (b) above are fully reversible within 7 days of observation.

CHAPTER 3.4

RESPIRATORY OR SKIN SENSITIZATION

3.4.1 Definitions and general considerations

3.4.1.1 *Respiratory sensitization* refers to hypersensitivity of the airways occurring after inhalation of a substance or a mixture.

Skin sensitization refers to an allergic response occurring after skin contact with a substance or a mixture.

3.4.1.2 For the purpose of this chapter, sensitization includes two phases: the first phase is induction of specialized immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e. production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitized individual to an allergen.

3.4.1.3 For respiratory sensitization, the pattern of induction followed by elicitation phases is shared in common with skin sensitization. For skin sensitization, an induction phase is required in which the immune system learns to react; clinical symptoms can then arise when subsequent exposure is sufficient to elicit a visible skin reaction (elicitation phase). As a consequence, predictive tests usually follow this pattern in which there is an induction phase, the response to which is measured by a standardized elicitation phase, typically involving a patch test. The local lymph node assay is the exception, directly measuring the induction response. Evidence of skin sensitization in humans normally is assessed by a diagnostic patch test.

3.4.1.4 Usually, for both skin and respiratory sensitization, lower levels are necessary for elicitation than are required for induction. Provisions for alerting sensitized individuals to the presence of a particular sensitizer in a mixture can be found in 3.4.4.2.

3.4.1.5 The hazard class “respiratory or skin sensitization” is differentiated into:

(a) Respiratory sensitization; and

(b) Skin sensitization

3.4.2 Classification criteria for substances

3.4.2.1 *Respiratory sensitizers*

3.4.2.1.1 *Hazard categories*

3.4.2.1.1.1 Respiratory sensitizers shall be classified in Category 1 where sub-categorization is not required by a competent authority or where data are not sufficient for sub-categorization.

3.4.2.1.1.2 Where data are sufficient and where required by a competent authority, a refined evaluation according to 3.4.2.1.1.3 allows the allocation of respiratory sensitizers into sub-category 1A, strong sensitizers, or sub-category 1B for other respiratory sensitizers.

3.4.2.1.1.3 Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for respiratory sensitizers. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table 3.4.1 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals.

Table 3.4.1: Hazard category and sub-categories for respiratory sensitizers

CATEGORY 1:	**Respiratory sensitizer**
	A substance is classified as a respiratory sensitizer: (a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or (b) if there are positive results from an appropriate animal test[1].
Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitization rate in humans based on animal or other tests[1]. Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitization rate in humans based on animal or other tests[1]. Severity of reaction may also be considered.

3.4.2.1.2 *Human evidence*

3.4.2.1.2.1 Evidence that a substance can lead to specific respiratory hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.

3.4.2.1.2.2 When considering the human evidence, it is necessary for a decision on classification to take into account, in addition to the evidence from the cases:

(a) the size of the population exposed;

(b) the extent of exposure.

3.4.2.1.2.3 The evidence referred to above could be:

(a) clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:

(i) *in vivo* immunological test (e.g. skin prick test);

(ii) *in vitro* immunological test (e.g. serological analysis);

(iii) studies that may indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated low-level irritation, pharmacologically mediated effects;

(iv) a chemical structure related to substances known to cause respiratory hypersensitivity;

(b) data from positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

3.4.2.1.2.4 Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance and development of respiratory hypersensitivity. Relevant information includes aggravating factors both in the home and workplace, the onset and progress of the disease, family history and medical history of the patient in question. The medical history should also include a note of other allergic or airway disorders from childhood, and smoking history.

3.4.2.1.2.5 The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. It is however recognized that in practice many of the examinations listed above will already have been carried out.

[1] *At present, recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.*

3.4.2.1.3 *Animal studies*

Data from appropriate animal studies[1] which may be indicative of the potential of a substance to cause sensitization by inhalation in humans[2] may include:

(a) measurements of Immunoglobulin E (IgE) and other specific immunological parameters, for example in mice;

(b) specific pulmonary responses in guinea pigs.

3.4.2.2 *Skin sensitizers*

3.4.2.2.1 *Hazard categories*

3.4.2.2.1.1 Skin sensitizers shall be classified in Category 1 where sub-categorization is not required by a competent authority or where data are not sufficient for sub-categorization.

3.4.2.2.1.2 Where data are sufficient and where required by a competent authority, a refined evaluation according to 3.4.2.2.1.3 allows the allocation of skin sensitizers into sub-category 1A, strong sensitizers, or sub-category 1B for other skin sensitizers.

3.4.2.2.1.3 Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for skin sensitizers as described in 3.4.2.2.2. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table 3.4.2 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals according to the guidance values provided in 3.4.2.2.2.1 and 3.4.2.2.3.2 for sub-category 1A and in 3.4.2.2.2.2 and 3.4.2.2.3.3 for sub-category 1B.

Table 3.4.2: Hazard category and sub-categories for skin sensitizers

CATEGORY 1:	**Skin sensitizer**
	A substance is classified as a skin sensitizer: (a) if there is evidence in humans that the substance can lead to sensitization by skin contact in a substantial number of persons, or (b) if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitization in humans. Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitization in humans. Severity of reaction may also be considered.

3.4.2.2.2 *Human evidence*

3.4.2.2.2.1 Human evidence for sub-category 1A can include:

(a) positive responses at ≤ 500 µg/cm^2 (HRIPT, HMT – induction threshold);

(b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;

(c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

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[1] *At present, recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.*

[2] *The mechanisms by which substances induce symptoms of asthma are not yet fully known. For preventative measures, these substances are considered respiratory sensitizers. However, if on the basis of the evidence, it can be demonstrated that these substances induce symptoms of asthma by irritation only in people with bronchial hyperreactivity, they should not be considered as respiratory sensitizers.*

3.4.2.2.2.2 Human evidence for sub-category 1B can include:

(a) positive responses at > 500 µg/cm^2 (HRIPT, HMT – induction threshold);

(b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure;

(c) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.

3.4.2.2.3 *Animal studies*

3.4.2.2.3.1 For Category 1, when an adjuvant type test method for skin sensitization is used, a response of at least 30% of the animals is considered as positive. For a non-adjuvant Guinea pig test method a response of at least 15% of the animals is considered positive. For Category 1, a stimulation index of three or more is considered a positive response in the local lymph node assay. Test methods for skin sensitization are described in the OECD Guideline 406 (the Guinea Pig Maximisation test and the Buehler guinea pig test) and Guideline 429 (Local Lymph Node Assay). Other methods may be used provided that they are well-validated and scientific justification is given. The Mouse Ear Swelling Test (MEST), appears to be a reliable screening test to detect moderate to strong sensitizers, and can be used as a first stage in the assessment of skin sensitization potential.

3.4.2.2.3.2 Animal test results for sub-category 1A can include data with values indicated in Table 3.4.3 below:

Table 3.4.3: Animal test results for sub-category 1A

Assay	Criteria
Local lymph node assay	EC3 value ≤ 2%
Guinea pig maximisation test	≥ 30% responding at ≤ 0.1% intradermal induction dose or ≥ 60% responding at > 0.1% to ≤ 1% intradermal induction dose
Buehler assay	≥15% responding at ≤ 0.2% topical induction dose or ≥ 60% responding at > 0.2% to ≤ 20% topical induction dose

3.4.2.2.3.3 Animal test results for sub-category 1B can include data with values indicated in Table 3.4.4 below:

Table 3.4.4: Animal test results for sub-category 1B

Assay	Criteria
Local lymph node assay	EC3 value > 2%
Guinea pig maximisation test	≥ 30% to < 60% responding at > 0.1% to ≤ 1% intradermal induction dose or ≥ 30% responding at > 1% intradermal induction dose
Buehler assay	≥ 15% to < 60% responding at > 0.2% to ≤ 20% topical induction dose or ≥ 15% responding at > 20% topical induction dose

3.4.2.2.4 *Specific considerations*

3.4.2.2.4.1 For classification of a substance, evidence should include any or all of the following using a weight of evidence approach:

(a) Positive data from patch testing, normally obtained in more than one dermatology clinic;

(b) Epidemiological studies showing allergic contact dermatitis caused by the substance; Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small;

(c) Positive data from appropriate animal studies;

(d) Positive data from experimental studies in humans (see Chapter 1.3, para. 1.3.2.4.7);

(e) Well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic;

(f) Severity of reaction may also be considered.

3.4.2.2.4.2 Evidence from animal studies is usually much more reliable than evidence from human exposure. However, in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification on a case-by-case basis. Normally, human data are not generated in controlled experiments with volunteers for the purpose of hazard classification but rather as part of risk assessment to confirm lack of effects seen in animal tests. Consequently, positive human data on skin sensitization are usually derived from case-control or other, less defined studies. Evaluation of human data must therefore be carried out with caution as the frequency of cases reflect, in addition to the inherent properties of the substances, factors such as the exposure situation, bioavailability, individual predisposition and preventive measures taken. Negative human data should not normally be used to negate positive results from animal studies. For both animal and human data, consideration should be given to the impact of vehicle.

3.4.2.2.4.3 If none of the above mentioned conditions are met, the substance need not be classified as a skin sensitizer. However, a combination of two or more indicators of skin sensitization as listed below may alter the decision. This shall be considered on a case-by-case basis.

(a) Isolated episodes of allergic contact dermatitis;

(b) Epidemiological studies of limited power, e.g. where chance, bias or confounders have not been ruled out fully with reasonable confidence;

(c) Data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in 3.4.2.2.3, but which are sufficiently close to the limit to be considered significant;

(d) Positive data from non-standard methods;

(e) Positive results from close structural analogues.

3.4.2.2.4.4 Immunological contact urticaria

Substances meeting the criteria for classification as respiratory sensitizers may in addition cause immunological contact urticaria. Consideration should be given to classifying these substances also as skin sensitizers. Substances which cause immunological contact urticaria without meeting the criteria for respiratory sensitizers should also be considered for classification as skin sensitizers.

There is no recognized animal model available to identify substances which cause immunological contact urticaria. Therefore, classification will normally be based on human evidence which will be similar to that for skin sensitization.

3.4.3 Classification criteria for mixtures

3.4.3.1 *Classification of mixtures when data are available for the complete mixture*

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by weight of evidence evaluation of these data. Care should be exercised in evaluating data on mixtures that the dose used does not render the results inconclusive. (For special labelling required by some competent authorities, see the note to Table 3.4.5 of this chapter and 3.4.4.2.)

3.4.3.2 *Classification of mixtures when data are not available for the complete mixture: bridging principles*

3.4.3.2.1 Where the mixture itself has not been tested to determine its sensitizing properties, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following agreed bridging principles. This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without the necessity for additional testing in animals.

3.4.3.2.2 *Dilution*

If a tested mixture is diluted with a diluent which is not a sensitizer and which is not expected to affect the sensitization of other ingredients, then the new diluted mixture may be classified as equivalent to the original tested mixture.

3.4.3.2.3 *Batching*

The sensitizing properties of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another untested production batch of the same commercial product when produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the sensitization potential of the untested batch has changed. If the latter occurs, a new classification is necessary.

3.4.3.2.4 *Concentration of mixtures of the highest sensitizing category/sub-category*

If a tested mixture is classified in Category 1 or sub-category 1A, and the concentration of the ingredients of the tested mixture that are in Category 1 and sub-category 1A is increased, the resulting untested mixture should be classified in Category 1 or sub-category 1A without additional testing.

3.4.3.2.5 *Interpolation within one category/sub-category*

For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same category/sub-category, and where untested mixture C has the same toxicologically active ingredients as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same category/sub-category as A and B.

3.4.3.2.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A + B;
(ii) C + B;

(b) The concentration of ingredient B is essentially the same in both mixtures;

(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);

(d) Ingredient B is a sensitizer and ingredients A and C are not sensitizers;

(e) A and C are not expected to affect the sensitizing properties of B.

If mixture (i) or (ii) is already classified by testing, then the other mixture can be assigned the same hazard category.

3.4.3.2.7 *Aerosols*

An aerosol form of the mixture may be classified in the same hazard category as the tested non-aerosolized form of the mixture provided that the added propellant does not affect the sensitizing properties of the mixture upon spraying.

3.4.3.3 *Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture*

The mixture should be classified as a respiratory or skin sensitizer when at least one ingredient has been classified as a respiratory or skin sensitizer and is present at or above the appropriate cut-off value/concentration limit for the specific endpoint as shown in Table 3.4.5 for solid/liquid and gas respectively.

Table 3.4.5: Cut-off values/concentration limits of ingredients of a mixture classified as either respiratory sensitizers or skin sensitizers that would trigger classification of the mixture

Ingredient classified as:	Cut-off values/concentration limits triggering classification of a mixture as:		
	Respiratory sensitizer Category 1		Skin sensitizer Category 1
	Solid/Liquid	Gas	All physical states
Respiratory sensitizer Category 1	≥ 0.1% (see note)	≥ 0.1% (see note)	--
	≥ 1.0%	≥ 0.2%	
Respiratory sensitizer Sub-category 1A	≥ 0.1%	≥ 0.1%	
Respiratory sensitizer Sub-category 1B	≥ 1.0%	≥ 0.2%	
Skin sensitizer Category 1	--	--	≥ 0.1% (see note)
	--	--	≥ 1.0%
Skin sensitizer Sub-category 1A	--	--	≥ 0.1%
Skin sensitizer Sub-category 1B	--	--	≥ 1.0%

NOTE: *Some competent authorities may require SDS and/or supplemental labelling only, as described in 3.4.4.2 for mixtures containing a sensitizing ingredient at concentrations between 0.1 and 1.0% (or between 0.1 and 0.2% for a gaseous respiratory sensitizer). While the current cut-off values reflect existing systems, all recognize that special cases may require information to be conveyed below that level.*

3.4.4 Hazard communication

3.4.4.1 General and specific considerations concerning labelling requirements are provided in *Hazard communication: Labelling* (Chapter 1.4). Annex 1 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Table 3.4.6 below presents specific label elements for substances and mixtures that are classified as respiratory and skin sensitizers based on the criteria in this chapter.

Table 3.4.6: Label elements for respiratory or skin sensitization

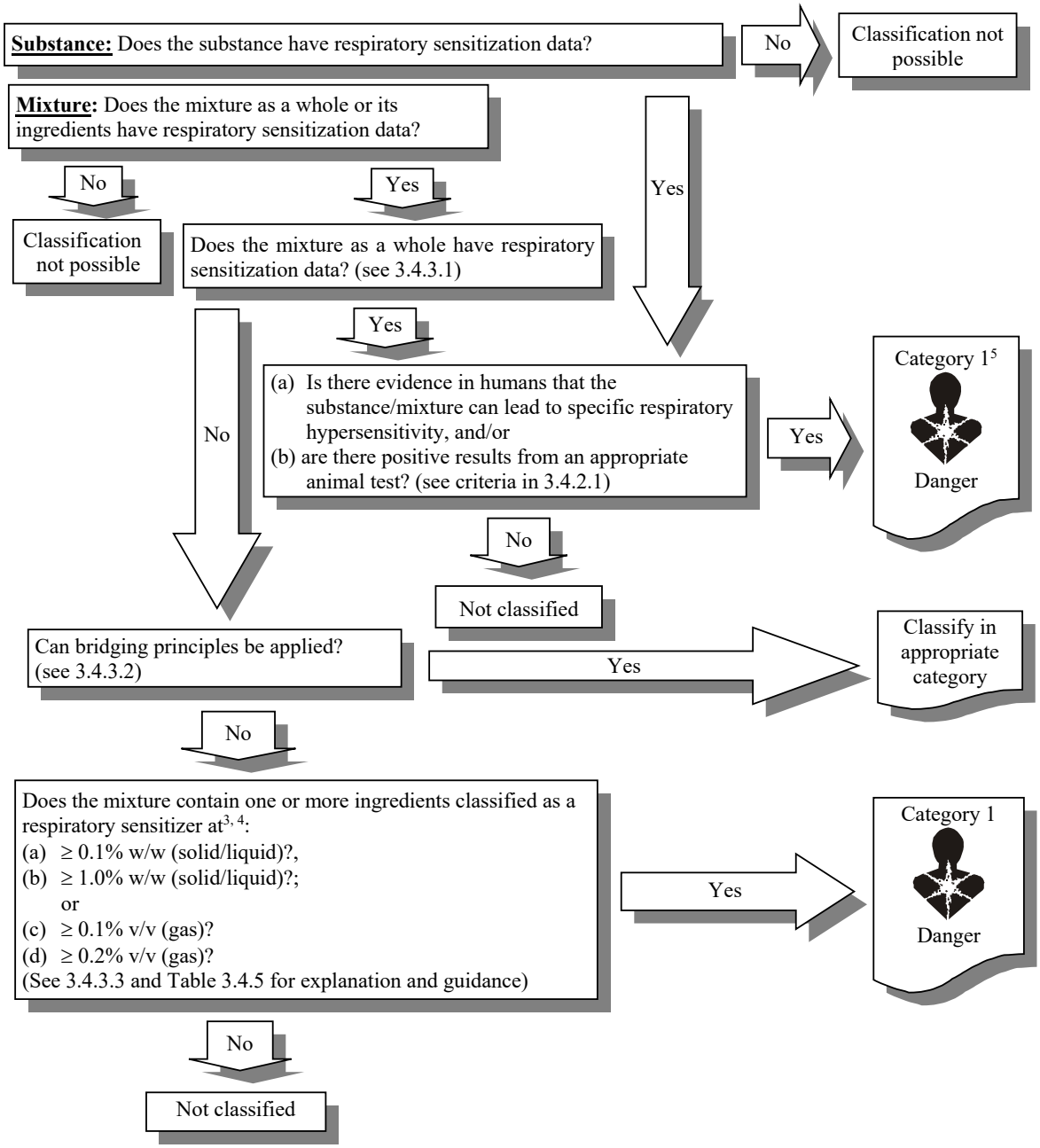
	Respiratory sensitization Category 1 and sub-categories 1A and 1B	Skin sensitization Category 1 and sub-categories 1A and 1B
Symbol	Health hazard	Exclamation mark
Signal word	Danger	Warning
Hazard statement	May cause allergy or asthma symptoms or breathing difficulties if inhaled	May cause an allergic skin reaction

3.4.4.2 Some chemicals that are classified as sensitizers may elicit a response, when present in a mixture in quantities below the cut-offs established in Table 3.4.5, in individuals who are already sensitized to the chemicals. To protect these individuals, certain authorities may choose to require the name of the ingredients as a supplemental label element whether or not the mixture as a whole is classified as sensitizer.

3.4.5 Decision logic

The decision logics which follow are not part of the harmonized classification system but are provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logics.

3.4.5.1 ***Decision logic 3.4.1 for respiratory sensitization***

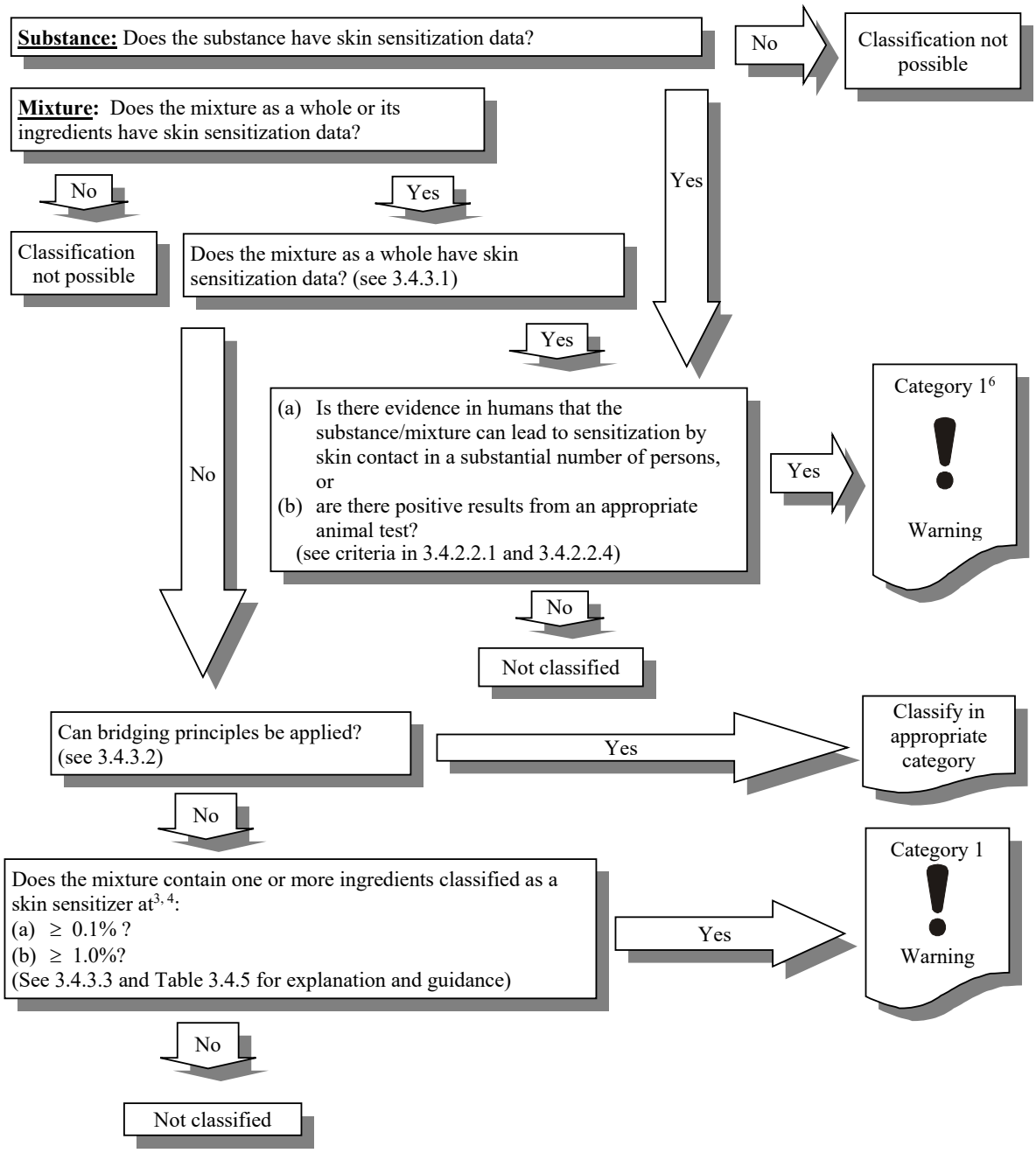


[3] *For specific concentration limits, see "The use of cut-off values/concentration limits" in Chapter 1.3, para. 1.3.3.2.*

[4] *See 3.4.4.2.*

[5] *See 3.4.2.1.1 for details on use of Category 1 sub-categories.*

3.4.5.2 ***Decision logic 3.4.2 for skin sensitization***



[3] *For specific concentration limits, see "The use of cut-off values/concentration limits" in Chapter 1.3, para. 1.3.3.2.*

[4] *See 3.4.4.2.*

[6] *See 3.4.2.2.1 for details on use of Category 1 sub-categories.*